Clinical Trial Designs for the First-line Hormonal Treatment of Metastatic Breast Cancer: Questions to the Committee

Questions about the comparator

- Toremifene, anastrozole, and letrozole were all approved by the FDA based on randomized clinical trials using tamoxifen as the comparator.
- Letrozole was approved by the FDA based on superiority to tamoxifen for response rate and time to progression. Toremifene and anastrozole were approved by the FDA based on non-inferiority to tamoxifen for response rate and/or time to progression (anastrozole demonstrated superiority in TTP in one small trial).
- There has been no direct comparison in the same randomized clinical trial of toremifene, anastrozole, or letrozole.

1a. Do the data presented allow the FDA to designate one hormonal drug as the comparator in future randomized clinical trials of new hormonal drugs for this use?

1b. If the answer to 1a is no, do the data presented allow the FDA to designate one class of hormonal drugs as the comparator in future randomized clinical trials of new hormonal drugs for this use?

Questions about the trial design

2. If the Committee believes that any first-line hormonal agent is an acceptable comparator, should new agents be required to demonstrate superior efficacy to tamoxifen, either by direct comparison to tamoxifen or by non-inferiority analyses compared to letrozole? What are acceptable comparators for non-inferiority designs?

Questions about the primary endpoint

3. Tamoxifen has not been demonstrated to affect time to progression or survival in randomized controlled trials. Because approval of subsequent hormonal therapies was based on non-inferiority or similarity to tamoxifen, TTP data are not available for these agents. Anastrozole demonstrated superior TTP to tamoxifen, but in a single small study; no difference was observed in a second larger study. Letrozole demonstrated superior TTP compared to tamoxifen; however, data from only a single trial are available to estimate effect size. A change in primary endpoint in the regulatory setting from response rate to TTP would require trial designs that demonstrate superiority to tamoxifen or non-inferiority to letrozole.

   For the first-line treatment of metastatic breast cancer with hormonal agents, should the traditional endpoint of response rate be replaced by TTP?

Questions about the definition of efficacy

4. In non-inferiority studies, it is important to know the size of the treatment effect of the comparator agent, and to decide on the amount of comparator effect that should be preserved when testing a new treatment. The estimate of the effect size, the amount of efficacy to be preserved, and the choice of endpoint influence the sample size of non-inferiority studies. Sample sizes may range from several hundred to many thousands of patients, depending on the combination of factors.

    a. Based on the Committee's clinical expertise, what amount of the comparator effect should be preserved in a non-inferiority trial of a new hormonal agent in the first-line treatment of metastatic disease? [Discussion only; no vote required]

    b. Does this assessment depend on whether RR or TTP is the primary endpoint?

General Questions

5. There are many ongoing studies of hormonal agents for the first-line treatment of metastatic breast cancer. Some of these studies are designed to demonstrate non-inferiority to tamoxifen and some are designed to demonstrate non-inferiority to other approved first-line agents from various classes of hormonal therapies, using response rate as the primary endpoint.

    Are there any potential trial designs that would need to be changed, based on your answers to the above questions?

[Discussion only; no vote required]

6. Please discuss whether these recommendations would change if patients treated with a hormonal therapy are found to have improved survival compared to patients treated with tamoxifen (with respect to comparator and endpoint).